Editorial

Angiotensin II receptor antagonists for heart failure

ACE inhibitors have revolutionised the treatment of chronic heart failure; however, as is often the case with drug treatment, we are remarkably ignorant of exactly how they work. Understanding the mechanisms involved is of fundamental importance because it is a major goal of pharmacological research to produce more specific drugs that act on the mechanism producing clinical benefit while having no effect on the mechanisms producing adverse effects. This ideal scenario seems to be a possibility if we substitute angiotensin II receptor antagonist drugs for ACE inhibitors. The rather optimistic idea behind this is that most if not all of the benefits of ACE inhibitors are because of angiotensin II suppression while the main adverse effect of ACE inhibitors (cough) is caused by bradykinin accumulation. How has practice lived up to this theory?

Basic pharmacological considerations

Angiotensin II exerts its effects by stimulating cell membrane receptors—AT_1 and AT_2 receptors. Virtually all of the recognised effects of angiotensin II are mediated by AT_1 receptors, which are blocked by AT_1 receptor antagonists. However, these drugs leave the AT_2 receptor unblocked and it is a concern that AT_2 receptors may be overstimulated by endogenous angiotensin II when AT_1 receptor antagonists are prescribed. However, it seems that AT_2 receptor stimulation in the presence of an AT_1 receptor antagonist may be beneficial, as AT_2 receptors appear to mediate antiproliferative effects and may even attenuate the proliferative effects of AT_1 receptor stimulation.[1] Clinical trials with AT_1 receptor antagonists have not uncovered any nasty surprises that could be attributed to AT_2 receptor stimulation. Clearly, if AT_2 receptor stimulation is beneficial, then AT_1 receptor antagonists should be better than ACE inhibitors because ACE inhibitors will lead to under stimulation of both AT_1 and AT_2 receptors.

ACE inhibitors not only suppress angiotensin II but they also lead to bradykinin accumulation. This is because the ACE enzyme has a much greater affinity for bradykinin than it does for angiotensin I (bradykinin K_m 0.85–1 μM; angiotensin I K_m 30–90 μM).[2] The accumulation of bradykinin is a double edged sword. On the debit side, bradykinin is likely to mediate the adverse effects of cough and perhaps angio-oedema; on the credit side bradykinin is likely to stimulate nitric oxide and prostacyclin release, which should improve endothelial function and may even have an antiatherosclerotic effect. However, other harmful effects of bradykinin accumulation have been described and are now attracting interest. The $64 000 question of whether AT_1 receptor antagonists will ever supersede ACE inhibitors may hinge largely, although not exclusively, on the balance between the beneficial and harmful effects of ACE inhibitor induced bradykinin accumulation.

Glossary
ACE: Angiotensin converting enzyme
CONSENSUS: Cooperative north Scandinavian enalapril survival study
ELITE: Evaluation of losartan in the elderly
SOLVD: Studies of left ventricular dysfunction

A third issue of pharmacological importance is that angiotensin II can be formed by routes other than angiotensin converting enzyme. Enzymes such as chymase, cathepsin G, and CAGE (chymostatin sensitive angiotensin II generating enzyme) seem able to generate angiotensin II by non-ACE routes.[3] We do not really know how big a contribution these non-ACE enzymes make to the production of angiotensin II but clearly ACE inhibitors will not prevent angiotensin II being formed from non-ACE enzymes, whereas AT_1 receptor antagonists will block the effect of angiotensin II, irrespective of which enzyme produced the angiotensin II. In this way, AT_1 receptor antagonists are likely to be able to block the effects of angiotensin II more effectively than ACE inhibitors can (table 1).

AT_1 receptor antagonists in hypertension

These theoretical benefits have led the pharmaceutical industry to develop a large number of AT_1 receptor antagonist drugs. These have initially been developed for the treatment of essential hypertension where they have generally fulfilled their promise of being safe, efficacious, and well tolerated. They appear to be better tolerated than other first line antihypertensive agents, including ACE inhibitors. In particular, the promise of their producing less cough than ACE inhibitors seems to have been fulfilled.[4] Indeed the incidence of all side effects of AT_1 receptor antagonist appears to be much the same as placebo, which cannot be said for any other class of antihypertensive drug. As you would expect, drug companies marketing AT_1 receptor antagonists are now trying to distinguish between the various agents. In hypertension, this is likely to focus on differences in antihypertensive efficacy, particularly differences in blood pressure control at trough drug concentrations. We are likely to be bombarded in the near future with data on this subject, but the jury is still out on whether any differences really exist.

AT_1 receptor agonists in heart failure

There are two major constraints in clinical trials with AT_1 receptor antagonists in heart failure. The first is ethical in that ACE inhibitors cannot be withheld from patients for long because of their undoubted clinical benefit. This means that clinical trials with AT_1 receptor antagonists cannot be done in the traditional way comparing the new drug with placebo. The second constraint is a genuine uncertainty about whether the future place of AT_1 receptor antagonists in heart failure will be as a substitute for ACE inhibitors or as an addition. This question remains wide open.

Table 1 AT_1 receptor antagonists versus ACE inhibitors

Possible advantages of AT_1 receptor antagonists
- AT_1 receptor antagonists prevent harmful effects of angiotensin II generated by non-ACE pathways
- Bradykinin release caused by ACE inhibitors might induce catecholamine release
- Bradykinin release caused by ACE inhibitors probably produce cough
- AT_1 receptor antagonists increase while ACE inhibitors reduce the antiproliferative effect of AT_2 receptor stimulation

Possible disadvantages of AT_1 receptor antagonists
- Bradykinin release caused ACE inhibitors might release nitric oxide and improve endothelial function
- AT_2 receptor stimulation might have unknown harmful effects

Until recently, clinical trials with AT_1 receptor antagonists in heart failure have in general shown that they exert the expected haemodynamic and neurohormonal effects. DeKock *et al* showed that single doses of losartan caused vasodilatation and reduced aldosterone and noradrenaline compared with placebo.[5] Crozier *et al* found that, compared with placebo, chronic losartan treatment (12 weeks) reduced pulmonary capillary wedge pressure, systemic vascular resistance, blood pressure, and even heart rate, while cardiac index rose.[6] In long term studies comparing losartan with enalapril, both drugs seemed equivalent in terms of exercise capacity, clinical status, neurohormonal activation and adverse effects.[7 8] Therefore, losartan as the prototype AT_1 receptor antagonist appeared to be as good as an ACE inhibitor, but there were no clear signs in heart failure that it might be any better. All that changed in early 1997 with publication of the ELITE trial results.[4]

ELITE TRIAL

The ELITE study was not intended to be a mortality study, rather it was a study of the safety of losartan in elderly patients with chronic heart failure. Therefore, we should view the mortality data from the ELITE study with scepticism. Nevertheless, the surprising finding was that losartan (50 mg/day) produced a 46% reduction ($p = 0.035$) in all cause mortality compared with captopril (50 mg three times daily). This difference was mainly because of a decrease in sudden deaths in the losartan group. Interestingly, losartan was also better tolerated than captopril, especially with regard to cough. Indeed, significantly more patients withdraw from captopril than from losartan (21% *v* 12%, $p = 0.002$). The benefits of losartan on all cause mortality could not be attributed to the greater withdrawal rate in the captopril group as there was an even greater mortality benefit (57% reduction) in those who remained on their study drug.

These results are, to say the least, intriguing. A second study is ongoing to see whether it can confirm this beneficial effect; ELITE II is a much larger trial with mortality as the primary end point. However, a recent unpublished study was unable to confirm the ELITE results.

Assuming that the ELITE results are genuine, why should losartan perform better than captopril? Clearly it could be related to pharmacology, which has been discussed above (table 1). The first possibility is that ACE inhibitors allow angiotensin II to be formed from non-ACE pathways. Data from the CONSENSUS and SOLVD studies show that patients who have high plasma concentrations of angiotensin II despite enalapril treatment have a worse prognosis than those with suppressed angiotensin II.[9 10] This could explain the ELITE results because patients with high angiotensin II concentrations despite ACE inhibitor treatment should benefit from blockade of the angiotensin II receptors, which would effectively neutralise the harmful effects of reactivated angiotensin II.

The second possibility is that the bradykinin produced by ACE inhibitors might be harmful rather than beneficial. Several studies attest to the fact that bradykinin can release noradrenaline, which could arrhythmogenic.[11 12] Such a mechanism might explain why losartan produced fewer sudden deaths than captopril in ELITE—that is, captopril increased bradykinin, which increased arrhythmogenic catecholamines.

Until these issues are resolved by ELITE II and other studies, what significance should the practising doctor attach to the original ELITE results. In view of all the beneficial trial data with ACE inhibitors, it would clearly be inappropriate to change large numbers of patients from ACE inhibitors to AT_1 receptor antagonists on the basis of one small trial; however, even a pessimist looking at the ELITE results is likely to think that AT_1 receptor antagonists may be equivalent to ACE inhibitors regarding mortality. The upshot is that patients who are truly intolerant of ACE inhibitors (especially because of cough) may well be able to get an equivalent mortality benefit if they are switched from an ACE inhibitor to an AT_1 receptor antagonist. This is a fairly small group of patients for whom hydralazine plus isosorbide dinitrate is a good alternative, with better documented mortality benefits. Nevertheless, it may be that heart failure patients who complain of ACE inhibitor cough should be switched to an AT_1 receptor antagonist rather than persuaded to continue the ACE inhibitor and tolerate the cough. The other tangible effect of the ELITE results is to engender a sense of hopeful expectation that this new class of drugs may well be as important a step in the management of heart failure as were ACE inhibitors.

Conclusions

The prospects are therefore good for AT_1 receptor antagonists, but there are more questions about these agents than there are answers. Many trials are underway that will provide these answers and that will tell us whether AT_1 receptor antagonists are likely to eclipse ACE inhibitors or whether they will turn out to be another blind therapeutic alley. The ELITE study suggests that the former is more likely than the latter.

A D STRUTHERS

Department of Clinical Pharmacology and Therapeutics,
Ninewells Hospital and Medical School,
Dundee DD1 9SY, UK

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